II. REMARKS

Formal Matters

Claims 1-9 and 15-19 are pending after entry of the amendments set forth herein.

Claims 1-9 and 15-18 were examined and were rejected. Claims 10-14 were withdrawn from consideration.

Claims 10-14 are canceled without prejudice to renewal, without intent to acquiesce to any rejection, and without intent to surrender any subject matter encompassed by the canceled claims. Applicants expressly reserve the right to pursue any canceled subject matter in one or more continuation and/or divisional applications.

Claim 19 is added. Support for new claim 19 is found in the claims as originally filed, and throughout the specification, including the following exemplary locations: paragraphs 0054-0065. Accordingly, no new matter is added by these new claims.

Applicants respectfully request reconsideration of the application in view of the remarks made herein.

Examiner Interview

The undersigned Applicants' representative thanks Examiner Venci and Examiner Le for the courtesy of a telephonic interview which took place on November 30, 2005, and which was attended by Examiners Venci and Le, inventor John Cooke, inventor Ken Lin, and Applicants' representative Paula A. Borden.

During the interview, the rejection of claims 1-9 and 15-18 under 35 U.S.C.§ 103(a), was discussed.

Rejections under 35 U.S.C.§103(a)

Claims 1-8 and 15-18 were rejected under 35 U.S.C.§103(a) as allegedly unpatentable over Balint and Cooke (WO 98/49199; "Balint") in view of Duerksen and Wilkinson ((1987) *Anal. Biochem.* 160:444; "Duerksen"). Claim 9 was rejected under 35 U.S.C.§103(a) as allegedly unpatentable over Balint and Duerksen and further in view of Fishman et al. (U.S. 5,318,680; "Fishman").

Claims 1-8 and 15-18 over Balint in view of Duerksen

The Office Action stated that:

1) Balint teaches a method of detecting ADMA in a sample comprising ADMA, SDMA, and arginine comprising the step of detecting ADMA;

2) Balint does not teach the step of "contacting the sample with an α-dicarbonyl compound";

3) Duerksen teaches the use of an α-dicarbonyl compound (OAPA) as a linker for immobilizing arginine-containing compounds to solid phases.

The Office Action stated that it would have been obvious for a person of ordinary skill in the art to modify the method of detecting ADMA of Balint with the use of OAPA, because "Duerksen & Wilkinson discovered that OAPA has the advantages of specificity, water solubility, negative charge, and linking ability." Office Action, page 2. Applicants respectfully traverse the rejection.

First, Duerksen is non-analogous art, and thus is not properly relied upon. Secondly, even if it were proper to rely upon Duerksen, the Office has not established a prima facie case of obviousness.

Duerksen is non-analogous art.

Duerksen is non-analogous art, and therefore is not properly relied upon. As noted in the MPEP §2141.01(a), in order to rely on a reference as a basis for rejection of an applicant's invention, the reference must either be in the field of the applicant's endeavor or, if not, then be reasonably pertinent to the particular problem with which the invention was concerned.[1] Duerksen is not in the field of detection of ADMA. Duerksen is not reasonably pertinent to the problem of detecting ADMA in a sample comprising ADMA, SDMA, and arginine. **Duerksen is concerned with protein immobilization**. Those skilled in the art, concerned with the problem of detecting ADMA in mixed samples including ADMA, SDMA, and arginine, would not have turned to Duerksen for a solution to the problem of detecting ADMA in mixed samples. Duerksen is concerned with **immobilizing proteins**, not with modifying arginines and SDMA.

The present situation is similar to the fact pattern presented in *In re Clay* (966 F.2d 656, 23 USPQ2d 1058 (Fed. Cir. 1992)). In *In re Clay*, claims were directed to a process for storing a refined liquid hydrocarbon product in a storage tank having a dead volume between the tank bottom and its outer port, where a gelled solution filled the tank's dead volume to prevent loss of stored product while

preventing contamination. One of the references relied upon disclosed a process for reducing the permeability of natural underground hydrocarbon-bearing formations using a gel similar to that used by the applicant, to improve oil production. The court disagreed with the Office's assertion that the reference and the claimed invention were part of the same endeavor ("maximizing withdrawal of petroleum stored in petroleum reserves"); instead, the court found that the inventions involved different fields of endeavor since the reference taught the use of the gel in a different structure for a different purpose under different temperature and pressure conditions, and since the application related to storage of liquid hydrocarbon rather than extraction of crude petroleum. The court also found that the reference was not reasonably pertinent to the problem with which the inventor was concerned, because a person having ordinary skill in the art would not reasonably have expected to solve the problem of dead volume in tanks for refined petroleum by considering a reference dealing with plugging underground formation anomalies.

The instant invention and Duerksen are in different fields of endeavor.

The instant invention is concerned with detection of ADMA in samples comprising ADMA, SDMA, and arginine. Methods of detecting ADMA have been hampered because previous methods were unable to distinguish between ADMA, and any SDMA and/or arginine that might also be present in the sample. The instant application addresses this problem by providing a method that includes modifying SDMA and arginine, but not ADMA, in such a way that the modified SDMA and arginine are readily distinguishable from ADMA.

Duerksen has nothing whatsoever to do with methods of detecting ADMA. Duerksen states: "A new method for activating polyacrylamide beads to bind proteins via arginine residues is described." Duerksen, page 444. Duerksen is in the field of **affinity chromatography** and **protein immobilization**; the instant application is in the field of **methods for detecting ADMA**.

Duerksen is not reasonably pertinent to the particular problem with which the invention was concerned.

Duerksen is not reasonably pertinent to the problem with which the instant claimed invention is concerned, because a person having ordinary skill in the art would not reasonably have expected to solve the problem of detecting ADMA in samples that might also contain SDMA and/or arginine by considering a reference dealing with affinity chromatography and protein immobilization.

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[1] *In re Oetiker*, 977 F.2d 1443, 1446, 24 USPQ2d 1443, 1445 (Fed. Cir. 1992)

The Office has not established a prima facie case of obviousness.

Even if it were proper to rely upon Duerksen -- and it is Applicants' position that it is not, as Duerksen is non-analogous art – the Office has not established a prima facie case of obviousness.

To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. *In re Fine*, 5 USPQ2d 1596 (Fed. Cir. 1988); *In re Jones,* 21 USPQ2d 1941 (Fed. Cir. 1992). Second, there must be a reasonable expectation of success. *In re Merck & Co., Inc.*, 231 USPQ 375 (Fed. Cir. 1986). Finally, the prior art reference, or references when combined, must teach or suggest all the claim limitations. *In re Roykа*, 180 USPQ 580 (CCPA 1974). All three criteria must be met. **If any one of these three criteria is not met**, a *prima facie* case of obviousness has not been established.

Balint, alone or in combination with Duerksen, cannot render instant claims 1-8 and 15-18 obvious, because:

1) There is no motivation or suggestion in Balint or in Duerksen, or in the knowledge generally available at the time of filing, to modify Balint or to combine Balint and Duerksen;
2) The cited references do not provide a reasonable expectation of success; and
3) Balint, alone or in combination with Duerksen, does not teach or suggest all of the claim limitations.

1. There is no motivation or suggestion in the cited references to modify Balint or to combine the teachings of Balint and Duerksen.

Balint discusses antibodies that are specific for ADMA, and detection methods using the antibodies. Balint discusses the problem of detecting ADMA in samples that include, in addition to ADMA, SDMA and arginine. Balint, page 7, lines 28-32. However, Balint does not propose any modifications of SDMA or arginine that would make these two compounds distinguishable from ADMA. Accordingly, there is no motivation in Balint to look to the teaching of Duerksen.

Duerksen does not provide any motivation to modify Balint, or to combine the teachings of Balint and Duerksen. Duerksen discusses a method of activating polyacrylamide beads to bind proteins

via arginine residues to the beads, using OAPA as a linking reagent. Nowhere does Duerksen discuss contacting a sample suspected of containing ADMA and at least one of SDMA and arginine with an α-carbonyl compound, so as to modify SDMA and arginine, such that the modified SDMA and the modified arginine are distinguishable from ADMA. Duerksen does not mention the problem of detecting ADMA in a sample that includes ADMA, SDMA, and arginine.

As noted in MPEP §2143.01, the mere fact that references can be combined or modified does not render the resultant combination obvious **unless the prior art also suggests the desirability of the combination.**[2] The Office Action stated that it would have been obvious to combine the reference teachings because Duerksen "discovered that OAPA has the advantages of specificity, water solubility, negative charge, and linking ability." Office Action, page 2. However, discovery of "specificity, water solubility, negative charge, and linking ability" does **not** provide motivation to combine the references. As recited in claim 1, the α-dicarbonyl compound modifies the guanidino nitrogens of SDMA and arginine such that they are distinguishable from ADMA. Duerksen is silent as to any reaction of an α-dicarbonyl compound with SDMA. Duerksen makes no mention of distinguishing modified arginine from ADMA. Accordingly, Duerksen does not provide any motivation to combine.

2. There is no reasonable expectation of success in the cited references.

As noted above, Balint discusses antibodies that are specific for ADMA, and detection methods using the antibodies. Balint discusses the problem of detecting ADMA in samples that include, in addition to ADMA, SDMA and arginine. Balint, page 7, lines 28-32. However, Balint does not propose any modifications of SDMA or arginine that would make these two compounds distinguishable from ADMA. As such, Balint does not provide any reasonable expectation of success of a method involving contacting a sample suspected of containing ADMA and at least one of SDMA and arginine with an α-carbonyl compound, so as to modify SDMA and arginine, such that the modified SDMA and the modified arginine are distinguishable from ADMA.

Duerksen does not provide a reasonable expectation of success. Duerksen does not discuss a method involving contacting a sample suspected of containing ADMA and at least one of SDMA and arginine with an α-carbonyl compound, so as to modify SDMA and arginine, such that the modified SDMA and the modified arginine are distinguishable from ADMA. There is no reasonable expectation of success in Duerksen that contacting sample suspected of containing ADMA and at least one of

SDMA and arginine with an α-carbonyl compound, would modify SDMA and arginine, such that the modified SDMA and the modified arginine are distinguishable from ADMA.

3. Balint, alone or in combination with Duerksen, does not teach or suggest all of the claim limitations.

Balint discusses antibodies that are specific for ADMA, and detection methods using the antibodies. Balint neither discloses nor suggests a method of detecting ADMA in a sample comprising ADMA, SDMA, and arginine, where the method involves contacting the sample with an α-dicarbonyl compound to modify the guanidino nitrogens of SDMA and arginine, where the modified SDMA and the modified arginine are distinguishable from ADMA.

Duerksen does not cure the deficiency of Balint. Duerksen discusses a method of activating polyacrylamide beads to bind proteins via arginine residues to the beads, using OAPA as a linking reagent. Duerksen reports that OAPA reacts with the arginine in the protein, and with aminated polyacrylamide beads, thereby coupling arginine-containing proteins to the beads. Duerksen, Abstract; and page 450, column 2; and page 452. Nowhere does Duerksen discuss contacting a sample suspected of containing ADMA and at least one of SDMA and arginine with an α-carbonyl compound, so as to modify SDMA and arginine, such that the modified SDMA and the modified arginine are distinguishable from ADMA.

Balint, alone or in combination with Duerksen, does not teach or suggest all of the claim limitations. Accordingly, Balint, alone or in combination with Duerksen, does not render claims 1-8 obvious.

Claim 9 over Balint and Duerksen in view of Fishman

The Office Action stated that:

1) Balint and Duerksen teach a method of detecting ADMA in a sample;
2) Balint and Duerksen do not teach a method using capillary electrophoresis;
3) Fishman teaches the use of capillary electrophoresis for derivatizing and separating sample components.

The Office Action stated that it would have been obvious for a person of ordinary skill in the art to perform the method of detecting ADMA in a sample, as taught by Balint and by Duerksen, with the

[2] *In re Mills*, 916 F.2d 680, 16 USPQ2d 1430 (Fed. Cir. 1990)

use of capillary electrophoresis because Fishman discovered that on-column derivatization results in fast kinetics and high yields. Applicants respectfully traverse the rejection.

As discussed above, claims 1-8 and 15-18 are not rendered obvious by Balint, alone or in combination with Duerksen. Fishman does not cure the deficiency of the combination of Balint and Duerksen. Fishman discusses capillary electrophoresis. However, Fishman neither discloses nor suggests a method of detecting ADMA, as claimed. Indeed, there is no mention in Fishman of a method of detecting ADMA. Accordingly, Fishman, alone or in combination with Balint and Duerksen, cannot render instant claim 9 obvious.

Conclusion as to the rejections under 35 U.S.C.§103(a)

Applicants submit that the rejection of claims 1-9 and 15-18 under 35 U.S.C. §103(a) has been adequately addressed in view of the remarks set forth above. The Examiner is thus respectfully requested to withdraw the rejection.

III. CONCLUSION

Applicants submit that all of the claims are in condition for allowance, which action is requested. If the Examiner finds that a telephone conference would expedite the prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

The Commissioner is hereby authorized to charge any underpayment of fees associated with this communication, including any necessary fees for extensions of time, or credit any overpayment to Deposit Account No. 50-0815, order number STAN-276.

Respectfully submitted,
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Date: January 13, 2006

By: _____
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